Medical Progress

Pathogenesis of Sarcoidosis

KARL VAN GUNDY, MD, *and* OM P. SHARMA, MD, *Los Angeles*

Sarcoidosis is a multisystem granulomatous disease of unknown etiology. The organs that are involved by sarcoidosis include the lungs in which the granuloma is seen in more than 90% of patients to the pituitary, which is only rarely affected. There are many hypotheses as to the cause of sarcoidosis. Some of them rely on the similarities seen between sarcoidosis and the other granuloma-forming diseases such as tuberculosis, berylliosis, pine pollen inhalation and acute and chronic bacterial and viral infections, while others find similarities between sarcoidosis and immune reactions observed in autoimmune disorders. Still other explanations implicate a genetic predisposition or a still-unknown agent as the underlying cause of the granuloma formation.

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What causes sarcoidosis remains a mystery. Despite a significant amount of research, the exact cause and factors that result in granuloma formation remain unknown. We review the typical sarcoid granuloma from its histologic features to the many hypotheses as to its origin. Also reviewed is the typical history of the granuloma from its primary formation to the development of end-stage fibrosis.

Sarcoid Granuloma

On histologic examination a lesion of sarcoidosis is a well-defined round or oval granuloma made up of compact, radially arranged epithelioid cells with pale-staining nuclei (Figure 1). These nuclei appear pale because the growth of the chromatin does not keep pace with the growth of the cytoplasm. The epithelioid cell, a modified macrophage, acquires its name because of its vague resemblance to an epithelial cell. The typical giant cell of the sarcoid granuloma is of the Langhans' type in which the nuclei are arranged in an arc or a circular pattern around a central granular zone. Lymphocytes may be found within the "tubercle" but are usually seen at the periphery. Caseation is absent; occasionally fibrinoid necrosis may be seen.[1] Fibrinoid necrosis is prominent in areas where several granulomas have coalesced and may be distinguished from caseation by the presence of a fine reticulin pattern on silver staining.[2]

What does this organized network of inflammatory cells of different origin guard so zealously? It has been suggested that the shape of a granuloma is the product of a perimeter defense that occurs when the inciting agent is small or circular, as in cases of tuberculosis, histoplasmosis, coccidioidomycosis and talc and beryllium granulomatosis.[3] It is conceivable that the sarcoid granuloma shrouds the mystery of a persistent, poorly degradable "antigen" of low potency. Indeed, this agent, if there is one, has an excellent survival record; it rarely kills the host!

Recently developed monoclonal antibody techniques and indirect immunofluorescence methods have given us a glimpse of the dynamic relationship between the various components of the granuloma and the putative causative agent. The center of the granuloma is composed of macrophage-derived cells and OK T4 helper lymphocytes, whereas the periphery of the granuloma has a large number of antigen-presenting interdigitating macrophages and OK T8 suppressor lymphocytes. The lymphokines from the inflammatory cells recruit blood-borne monocytes, prevent macrophage migration and keep the chronic inflammatory reaction alive and efficient (Figure 2). It is probable that this arrangement of interdigitating OK T8 cells in the periphery and the epithelioid cell-OK T4 pattern in the center does indeed provide an efficient response to a persistent antigenemia. We and others have found this efficient architectural arrangement in cases of tuberculoid leprosy and those in which an efficient immune system keeps the bacillary load to a minimum; in lepromatous leprosy, on the other hand, the arrangement of the immune cells is disorganized and haphazard and bacteria flourish merrily.[4,5]

Natural History of a Sarcoid Granuloma

If a granuloma does not resolve spontaneously or after adequate therapy, it becomes converted into avascular, almost acellular, connective tissue. Granulomas that persist longer than a year or two show peripheral hyalinization and some fibrosis. In late stages complete hyalinization and fibrosis result in tissue scarring.

The mechanisms regulating the development of fibrosis are not well understood,[6] but it stands to reason that if the "antigen" is eliminated, the granuloma will disappear; if it persists, fibrosis will occur. In this drama, alveolar macrophages seem to play an important role by producing a number of active mediators, including a macrophage factor or alveolar macrophage-derived fibroblast growth factor that activates fibroblasts, fibronectin, biologically active factor VII and interleukin-1. The role of lymphocyte products such as interleukin-2 and γ-interferon is unclear. Prostaglandins (PGE_2) appear to modulate fibroblast growth. Neutrophils may be involved in the pathogenesis of fibrosis. The cells are

From the Department of Medicine, Pulmonary Disease Section, Sarcoidosis Clinic, Los Angeles County-University of Southern California Medical Center, Los Angeles. Reprint requests to Om P. Sharma, MD, Pulmonary Disease Service, Room 11-900, LAC-USC Medical Center, 1200 N State St, Los Angeles, CA 90033

ABBREVIATIONS USED IN TEXT

BAL = bronchoalveolar lavage
HLA = human leukocyte antigen
Ig = immunoglobulin
PG = prostaglandin
SLE = systemic lupus erythematosus

recruited from peripheral blood by a macrophage-derived factor. These lung neutrophils may participate in the development of fibrosis by producing either superoxide anion or by influencing immune complexes.[6]

Organ Involvement and Functional Derangement

No body tissue is exempt from sarcoidosis. Functional disturbances and physiologic abnormalities reflect the organ involvement by the disease and are due to interference of the organ function by the granuloma or fibrosis.

Lungs

The lungs are affected in more than 90% of the patients with sarcoidosis. The pulmonary granulomas have a predilection for peribronchial, subpleural and interlobular septal connective tissue. The alveolar septa when infiltrated with inflammatory cells and fibroblasts become firm and distorted. The blood vessels are involved in as many as 92% of all cases, but clinical pulmonary hypertension is rare. The bronchial and bronchiolar mucosa is commonly involved. Extensive fibrosis in advanced stages results in honeycomb lung and cor pulmonale. Aspergilloma may occur in cystic bronchiectatic cavities or bullous emphysema.

Extensive physiologic studies in the past emphasized functional changes characteristic of "restrictive impairment." Vital capacity, residual volume and total lung capacity are reduced. The loss of diffusing capacity remains perhaps the most common abnormality in sarcoidosis. The diffusing capacity is reduced even in patients with hilar adenopathy without any associated parenchymal infiltrates on chest x-ray film (stage 1).[7] Severe abnormalities of gas exchange also are more frequent than is generally realized. No single test, however, or combination of lung function, arterial blood gas values or pulmonary symptoms can precisely predict exercise limitation in sarcoidosis patients.[8] The obstruction of airways—large and small—is quite common in sarcoidosis.[9,10] The abnormality may result from either one or any combination of the following three factors: endobronchial granulomas and bronchiolitis; fibrosis and disruption of the supporting structure around the airways, or release of chemical mediators, complement products and anaphylotoxins from activated alveolar macrophages. Histamine concentrations in lavage fluid from patients with sarcoidosis are increased. The presence of airways obstruction may indicate persistent and extensive disease.

Lymphatic System

Involvement of the peripheral and other lymph node clusters, such as retroperitoneal nodes, varies from 32% to 78%. For obvious reasons, higher figures for lymph node involvement are observed at autopsy (Figure 3). In lymph nodes the granulomas may replace the whole gland structure or may show patchy involvement with areas of relatively normal lymph node architecture. Lymphatic obstruction a la elephantiasis is extremely rare.

Liver

The liver is palpable in only 20% of patients with sarcoidosis, but granulomas are observed in 63% to 87%, depending on the stage and activity of the disease. The differential diagnosis of hepatic granuloma, particularly in the absence of any

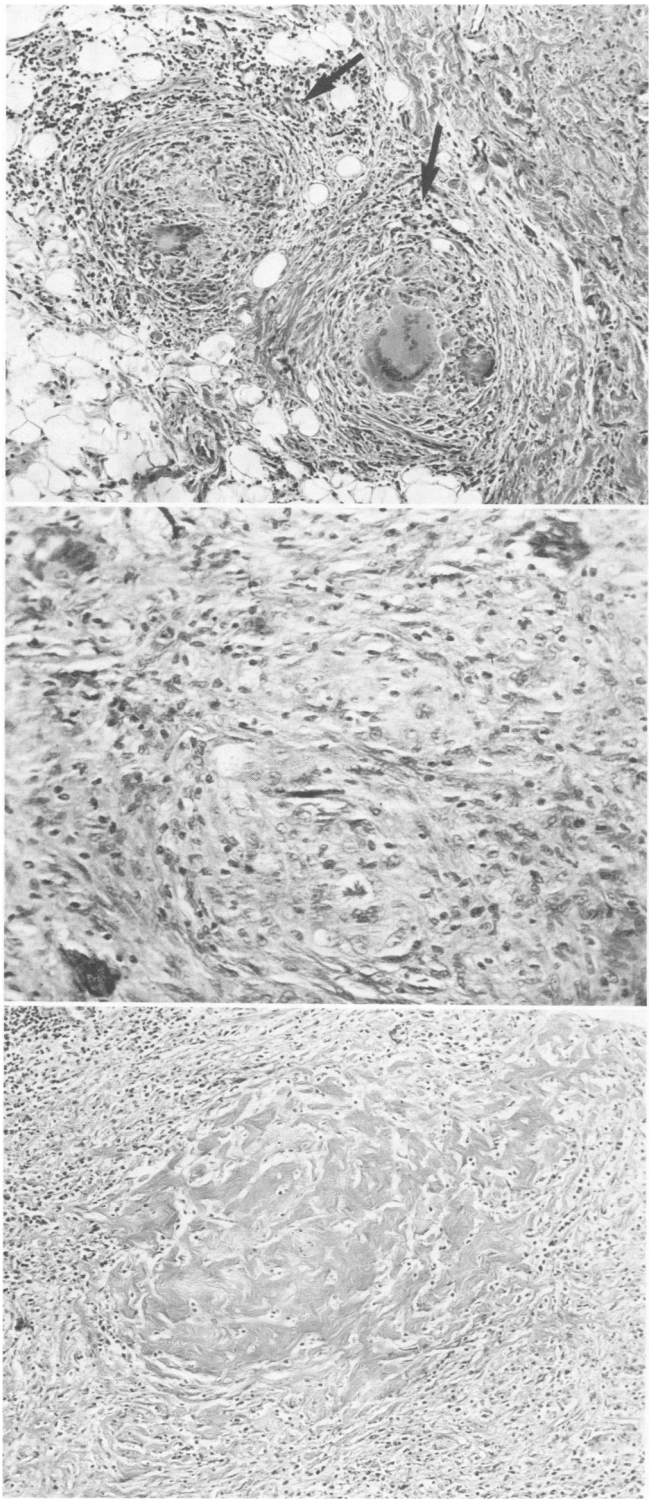

Figure 1.—Top, A sarcoid granuloma shows compact epithelioid cells **(arrows)** with scanty rims of lymphocytes and multinucleate giant cells (hematoxylin-eosin stain, original magnification x 200). **Middle,** An asteroid body is shown inside a granuloma (hematoxylin-eosin stain, original magnification x 200). **Bottom,** The microphotograph shows late-stage granuloma with hyalinization (hematoxylin-eosin stain, original magnification x 300).

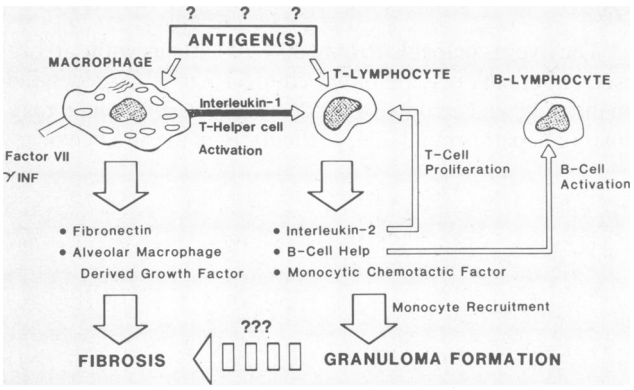

Figure 2.—The schema shows the pathogenesis of pulmonary sarcoidosis. γINF = γ-interferon

evidence of multisystem sarcoidosis, requires an extensive search for acid-fast organisms, other bacteria and fungi, cytomegalovirus, schistosomiasis, primary biliary cirrhosis, lymphoma and neoplastic disorders. Mild elevations of alkaline phosphatase and serum bilirubin levels are common; severe jaundice is infrequent, and portal hypertension is extremely rare (Figure 4).

Spleen

The incidence of a palpable spleen varies from 1% to 42%, but splenomegaly is noticed more frequently at autopsy. Splenic involvement is usually silent; occasionally it may cause pressure symptoms or hypersplenism.

Myocardium

At autopsy myocardial granulomas are found in about a quarter of all patients with sarcoidosis. The granulomas most commonly involve the left ventricular septum. Aorta, pulmonary artery, superior vena cava and pulmonary veins are infrequently affected. The pericardium and the valves are rarely involved. Because of the patchy distribution of the granulomas, an endomyocardial biopsy is of limited value.

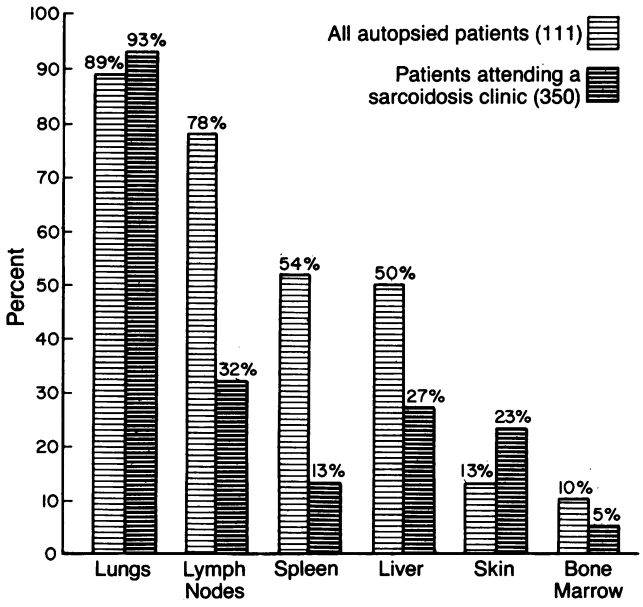

Figure 3.—The graph shows the frequency of various tissue involvement in 111 autopsied cases of sarcoidosis as compared with 350 patients attending the Sarcoidosis Clinic at Los Angeles County-University of Southern California Medical Center.

Eyes

The most common of eye lesions is granulomatous uveitis. Acute uveitis tends to clear spontaneously, but progressive uveal tract inflammation may cause adhesions between the iris and the lens, glaucoma, cataract and blindness. Periphlebitis retinae, retinal hemorrhage, retinitis proliferans, band keratopathy, proptosis and exophthalmos are some of the other uncommon manifestations of ocular sarcoidosis.

Skin

The most specific cutaneous sarcoidosis lesion is lupus pernio. It consists of a raised, violaceous, indurated plaque affecting the nose, the surrounding area of the face and the nasal mucosa. Ulceration is rare.[11]

Other Organs

Almost any organ can be involved. Kidney involvement may lead to the nephrotic syndrome, uremia and renal failure. Hypercalcemia or hypercalciuria may result in nephrocalcinosis or symptomatic renal stones. Bones and joints are affected, but crippling arthritis is uncommon. Sarcoidosis bone cysts are collections of sarcoid granulomas surrounded by a zone of osteoclastic reabsorption. Bone lesions are related to neither serum protein nor calcium levels. Sarcoid granulomas may also be found in meninges, brain substance, hypothalamus, pituitary gland, spinal cord and cranial and peripheral nerves. The rare association of thyroiditis, Addison's dis-

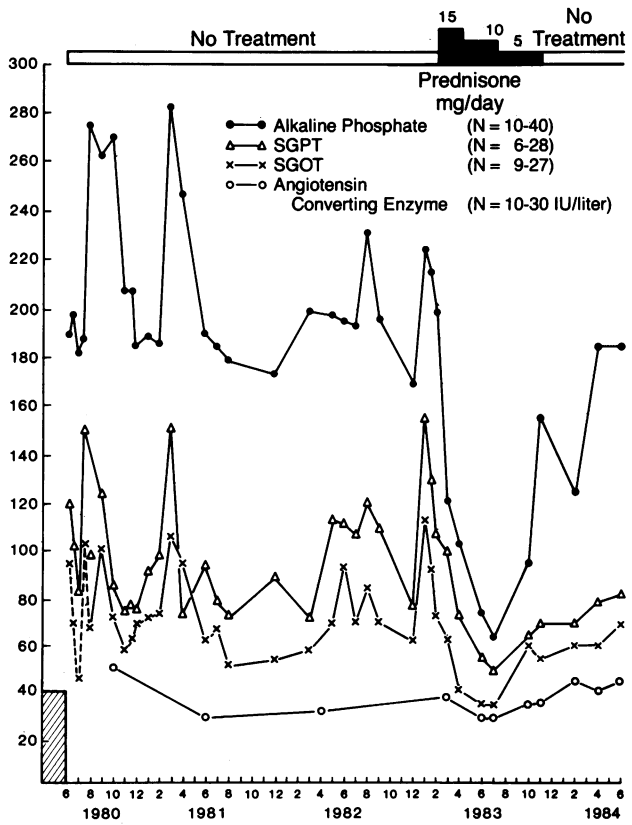

Figure 4.—The graph shows liver function fluctuations in a woman with asymptomatic granulomatous hepatitis. Even a small dosage of prednisone may induce the dramatic normalization of various tests. Mildly abnormal liver function tests in an asymptomatic person do not constitute an indication for corticosteroid therapy. SGOT = serum glutamic-oxaloacetic transaminase, SGPT = serum glutamic-pyruvate transaminase

ease, Sjögren's syndrome and sarcoidosis is popularly known as the TASS syndrome.[12]

Cause of Sarcoidosis

What causes sarcoidosis remains a mystery. Hypotheses abound; some are of only historical interest and others merely speculative. Is it a clinical syndrome with many causes, or is it a disease produced by a lone perpetrator? From time to time we have pointed a finger at the following as the etiologic agent of sarcoidosis.

Mycobacterium tuberculosis

The theory of a tuberculous cause of sarcoidosis became popular because of the similarities between the two granulomas and the occasional occurrence of tuberculosis before, during or after the identification of sarcoidosis.[13-16] Bowman and associates, however, failed to isolate bacteria, fungi, *Mycoplasma* or acid-fast organisms from patients with confirmed sarcoidosis.[17] Chapman and Speight suggested that sarcoidosis was a hypersensitivity reaction to atypical mycobacteria.[18] They found elevated antibody titers to atypical mycobacteria in more than 90% of the patients with sarcoidosis. Others have failed to duplicate these findings. Most authorities now agree that there are vast epidemiologic, clinical, radiologic and immunologic differences between sarcoidosis and tuberculosis.[19,20] The theory that sarcoidosis resulted from tissue activation of phage-infected lysogenic mycobacteria never became popular because of the inability of several workers to reproduce the findings reported by Mankiewicz and co-workers.[21-26] Most authorities now agree that the cause of sarcoidosis is neither tuberculosis nor a mycobacteriophage.

Other Infectious Causes of Sarcoidosis

Many known viruses such as mumps, influenza, Newcastle and some uncommon viruses have been implicated as a cause of sarcoidosis.[27-30] Richters and colleagues found ovoid bodies within the mitochondria.[29] They also noted linear densities in the membranes of dilated cisternae that resembled the partial expression of indigenous organisms. Steplewski and Israel cultured biopsy specimens of sarcoid-involved lymph nodes and postulated that the abnormal growth of the fibroblasts suggested that a viral agent was present.[31] In each of these cases, however, the workers were not able to transfer this reaction with supernatant transfer, neither were they able to grow or show true viral activity.[32-34] To this date, there has been no convincing evidence of a viral cause.

Mycoplasma orale has also been found in a greater-than-chance correlation with the incidence of sarcoid.[35,36] The causal relationship still has not been found. Uesaka and coworkers implicated *Nocardia* or an organism similar to it as a possible cause of sarcoid and were able to identify the organism in scalene and mediastinal lymph node specimens from patients who had sarcoidosis.[37] A fungal agent causing sarcoid is a rare phenomenon.

Noninfective Agents

Many noninfective causes of sarcoidosis have been considered. Beryllium was proposed as a cause of sarcoid first by Gentry and associates in 1955 and by several investigators after that.[38-40] The clinical differences between chronic beryllosis and sarcoidosis are many (Table 1). Cummings and Hudgins proposed that inhaling pine pollen was a causal factor in the development of sarcoidosis because the pine pollen induced epithelioid cell granulomas in tuberculin-sensitive guinea pigs.[41,42] Baer proposed that the habit of chewing pine needles was a cause.[43] Other investigators have proposed numerous agents as a cause of sarcoidosis including peanut dust, hair sprays, eating clay, zirconium exposure, mineral oil, talc powder and the use of phenylbutazone, sulfonamide or methotrexate. But in none of these or in others have further epidemiologic studies and investigations been able to substantiate the claims or prove an absolute correlation.[39,40,44-54]

TABLE 1.—*Some Features of Sarcoidosis and Chronic Beryllium Disease*

Feature	*Sarcoidosis*	*Chronic Beryllosis*
Occupational exposure	No	Metal/alloy/ceramics
Onset	Acute or insidious	Insidious
Erythema nodosum	Frequent	No
Hilar lymphadenopathy	Frequent	Rare
Uveitis	20% to 25%	Rare
Granuloma	Noncaseating	Noncaseating
Kveim test	Positive	Negative
Beryllium skin test	Negative	Positive
Angiotensin-converting enzyme	Increased (60%)	Normal
Genetic background	HLA-B8/A1/Cw7/DR3	Not known
Prognosis	Good	Poor

HLA=human leukocyte antigen

Genetic Predisposition

There is an uneven distribution of sarcoidosis throughout the world, with the highest prevalence of the disease among blacks in the United States, Irish and West Indians in London and Puerto Ricans in the New York metropolitan area. This suggests the possibility of some yet-unrecognized genetic and environmental predisposition to the development of sarcoidosis.[55,56]

There is a considerable variance in human leukocyte antigen (HLA) markers associated with sarcoidosis in different parts of the world. Tachibana and colleagues reported an increase in HLA-DR MT2 and HLA-Bw61 in Japanese patients with sarcoid.[57] Thunell and co-workers found an increase in HLA-B8 in patients with erythema nodosum and early sarcoidosis and an increase in HLA-B27 in Swedish patients with advanced sarcoid.[58] Möller and associates could find no association between HLA-B7 phenotypes and sarcoidosis in German patients.[59] Others have been unable to show similar associations or disassociation with various HLA markers.[60-63]

Other environmental factors may influence the occurrence of sarcoidosis such as smoking, which may decrease the risk for sarcoidosis developing, especially in young black women. Harf and colleagues compared the smoking habits of patients with sarcoidosis and found a significant protective effect of smoking.[64] Some studies have reported as high as a fourfold increase in the occurrence of sarcoidosis in nonsmokers as in smokers. There is also an increase in the protective effect of smoking with increasing use. Others have found similar protective effects from smoking but not to the same degree as was reported by Harf and co-workers.

Lawrence and associates found that the percentage of total lymphocytes in a bronchoalveolar lavage (BAL) specimen was significantly reduced in normal smokers but not in pa-

tients with sarcoid who smoked.[65] They also observed that a nonsmoking sarcoid patient's BAL specimen showed a decreased percentage of suppressor (T8) lymphocytes and a decrease in the T4:T8 ratio as compared with normal nonsmokers. Katz and Fauci reported that the total number of lymphocytes in the serum was reduced, with an increase in the proportion of suppressor (T8) lymphocytes in all patients with sarcoidosis.[66] Crystal and colleagues reviewed the BAL specimens of patients with sarcoid and found that there is an increase in the number of activated T lymphocytes within the alveolar structures and that the lung T lymphocytes of patients with sarcoid release mediators such as monocyte chemotactic factor.[67] Others have found that the specimens of BAL from patients with sarcoidosis are significantly higher in such agents as immunoglobulin (Ig) A, C3, α_1-antitrypsin, fibronectin and β_2-macroglobulin. The development of sarcoidosis is perhaps induced or aggravated by some or all of these agents; the mechanism by which this occurs is by the activation of blood monocytes in the lung or by increasing and promoting an inflammatory reaction in the pulmonary system.[68,69]

Autoimmune Disease

Sarcoidosis has at least a partial autoimmune origin.[70,71] Serum IgG values are elevated in 50% of the patients with sarcoid, IgM levels are raised in 25% and IgA levels are elevated in 10%.[72] There are, however, many similarities between sarcoidosis and many of the collagen vascular diseases, especially progressive systemic sclerosis and systemic lupus erythematosus (SLE). In an extensive review of the literature, however, Wiesenhutter and Sharma found only seven reported cases of sarcoidosis coexisting with a collagen vascular disease.[73] Telium reported on the similarity between systemic lupus erythematosus and sarcoid and showed that common to both diseases are hyperglobulinemia and the development of hyalin deposition in the reticuloendothelial system.[71] He also proposed that the development of the granuloma in sarcoidosis is due to the deposition of γ-globulins in response to an immune stimulus. Similar abnormalities have been described in some of the other collagen vascular disorders. Explanations for them have been many, such as a specific defect in the suppressor T cells, permitting the release of a "non-self" clone that causes an organ-specific reaction, abnormal activation of B cells or the abnormal activation of both of these immune systems at the same time.[74] As a further argument that an immune reaction is somehow involved in the formation of sarcoid granulomas is the finding of multiple immunologic changes in many of these diseases. Uveitis is frequently seen in patients with progressive systemic sclerosis or SLE and in 20% to 25% of patients with sarcoidosis.[75-77] As many as 50% of the patients with Sjögren's syndrome have an associated connective tissue disease.[78] Turiaf and Battesi felt that the oculosalivary involvement seen in Sjögren's syndrome can occur in patients with sarcoidosis and at times it may be a subclinical presentation of sarcoidosis.[79] In about 50% of patients with primary biliary cirrhosis, noncaseating granulomas are found. Primary biliary cirrhosis has been reported in conjunction with Sjögren's syndrome, the syndrome of calcinosis cutis, Raynaud's phenomenon, sclerodactyly and telangiectasia and with renal tubular acidosis. Sarcoidosis and autoimmune diseases may have a common origin with Sjögren's syndrome.[20]

Increase in the number of peripheral B lymphocytes and null cells is seen in SLE and sarcoidosis. Cutaneous sensitivity and the lymphocyte response to mitogens (in vitro) are decreased in both SLE and sarcoidosis. A decrease in the number of peripheral T lymphocytes is seen in patients with SLE, progressive systemic sclerosis and sarcoidosis; monocytes are hyperbasophilic and activated in cases of these disorders. A positive antinuclear antibody test is seen in 5% to 30% of patients with sarcoidosis, and a positive rheumatoid factor is seen in 20% to 40% of patients with the disorder. Serum and tissue immune complexes are frequently seen in patients with sarcoidosis, especially if erythema nodosum is present.[72]

Most, if not all, patients with the organ-specific autoimmune disorders, such as Graves' disease, idiopathic Addison's disease, Hashimoto's thyroiditis, Sjögren's syndrome, idiopathic thrombocytopenic purpura, myasthenia gravis, scleroderma and primary biliary cirrhosis, have hyperglobulinemia, which occasionally may coexist with sarcoidosis.[74,80] They also occasionally have nonspecific circulating antibodies and some, if not all, do respond to some extent to corticosteroid therapy, as do patients with sarcoidosis. Additional immunologic disorders that have been associated with sarcoidosis include autoimmune-induced thyroiditis,[81] vitiligo and pernicious anemia.[12,82]

Hematologic abnormalities are common to both sarcoidosis and autoimmune diseases, the most common one being thrombocytopenia.[83,84]

Amyloidosis is rare in patients with sarcoidosis; when it occurs, it may be related to the immune reaction and hypergammaglobulinemia.[85-89] A possible explanation as to why the prevalence of amyloidosis is not higher in patients with sarcoid is that as many as 80% of the patients in whom sarcoid develops will have resolution of their disease in less than two years and thus the disease may not exert a long enough or strong enough antigenic stimulus to induce the formation of secondary amyloidosis.[89]

Sarcoidosis frequently involves the pulmonary vasculature.[90,91] With the pulmonary capillary tunica propria being involved about 50% of the time, the endothelial cells are enlarged in 80% of the patients affected with sarcoidosis, and perivascular edema is seen in 60% of these patients.[92,93] In some with sarcoidosis in whom widespread granulomatous vasculitis develops, the vasculitis itself may play a role in the development of sarcoidosis.

The higher antibody response and immune complexes usually occur in the early acute stages of the disease[94,95] and may actually represent a better prognosis. Further associations between immune diseases and sarcoidosis remain to be proved. There are just as many or more differences between sarcoidosis and autoimmune disorders, including many clinical, radiologic and immunologic ones, that preclude vasculitis or autoimmune disorders as the major causes of sarcoid.

Cancer

Noncaseating granulomas are occasionally seen in patients with certain malignant disorders. Bronchogenic carcinoma was described in 1954 by Jefferson and associates[96] and later reported by others as having many similarities with sarcoidosis.[97-101] Granulomas have been described in patients after radiation therapy and after chemotherapy.[101] Sarcoidosis has occasionally been confused with lymphomas and carcinomas because of radiographic similarities such as bilateral hilar adenopathy.[100,101] There have been a few reports of

the coexistence of Hodgkin's lymphoma or bronchogenic carcinoma and sarcoidosis in the same patient.[102] Although sarcoidosis and Hodgkin's disease have certain common clinical and immunologic features, so far no convincing etiologic relationship has been established.[103-106]

The question as to whether the immunologic defect in sarcoidosis may in some way lead to the development of Hodgkin's disease or that a common virus may induce either of the diseases is still speculative. Brincker and later Brincker and Wilbek found that the incidence of malignant lymphoma was 11 times more common in patients with sarcoidosis than in the general population.[107,108] But studies done by Romer and again by James failed to confirm this increased incidence.[109,110] By applying strict diagnostic criteria with a thorough evaluation of patients, it is relatively easy to distinguish between the granulomas caused by malignant disorders, radiation therapy and chemotherapy and the multisystem disease called sarcoidosis.

Conclusion

There are many unanswered questions about sarcoidosis. In which organ does the disease originate? How does it disseminate? Considerations are that sarcoid spreads through either a hematogenous or a lymphatic route, or that it originates from either a hypersensitivity reaction or a vasculitis. It is possible that the initial alveolar injury that results in the formation of the immune and inflammatory reaction in sarcoidosis is caused by an inhaled antigen. After this stimulus the alveolitis may either resolve or remain dormant indefinitely, or it may become chronic, resulting in persistent granuloma formation and fibrosis. The exact antigen or antigens that cause the initiation of the alveolitis remain obscure, but the formation and perpetuation of the granuloma are carried out by activated T cells. The presence of hyperglobulinemia, defective suppressor T-cell function, loss of self-tolerance to self-antigens with the appearance of autoantibodies, uveitis and the favorable response to immunosuppressive therapy suggest that an autoimmune mechanism plays an important role in the pathogenesis of sarcoidosis. The expression of the sarcoid granuloma may be influenced by hormonal or environmental stimuli. A genetic predisposition or genetic abnormality may play a role in the expression of the disease. Okabe and colleagues have recently shown chromosomal aneuploidy in the granuloma cells.[111] The stimulus for the formation of the aneuploidy chromosomes formation can be speculated as originating from a chromosomal abnormality or the desuppression of opsonin, or it may be due to a bacteriophage that has not yet been isolated. It is conceivable that an environmental agent may stimulate the formation of the aneuploidy cell and the formation of sarcoidosis. On the other hand, it is just as possible that chromosomal aneuploidy may be totally unrelated to granuloma formation.

The pathogenesis of sarcoidosis is still undefined, but with the facilities now at our disposal in the field of electron microscopy, virology and immunology, we should be able to pin down the etiologic agent in the not-too-distant future.

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